Effect of Salbutamol, ipratropium bromide and Beclomethasone on Bronchial Asthma

Md. Ali Hossain, FCPS[1], **Md. Rashidul Hassan,** FCPS[2], **M. Khurshidul Islam,** DTCD[3], **A.K.M. Moslehuddin,** FCPS[4]

Summary :

Asthma is a common and chronic inflammatory condition of the airways and its prevalence in Bangladesh is not less than any other reported figures in the world. Various therapeutic regimens have been advocated for the management of bronchial asthma with varying success. Very few studies have been done with salbutamol, ipratropium and beclomethasone combinations. The present study was designed to find out the relationship and effects of salbutamol, ipratropium and beclomethasone in bronchial asthma. In the present study it was observed that all the parameters of pulmonary functions improved significantly with salbutamol, with ipratropium only PEF (Peak expiratory flow) was significantly improved, with salbutamol- ipratropium and salbutamol ipratropium- beclomethasone all parameter of pulmonary functions improved significantly.

Introduction :

Bronchial asthma is a common respiratory disorder which can affect people of any age group and patient may suffer from mild to severe form of illness[1]. It represents one of major health problem both in terms of human sufferings and in cost to Society in the form of lost productivity and requirements to health care resources. The prevalence and incidence of asthma is difficult to assess with certainty because of the lack of reliable population based data that have used uniform diagnostic criteria. The overall worldwide prevalence of asthma is 2.5%[2]. About one third of asthma patients are first diagnosed after 30 years of age[3]. 45.83% of all respiratory cases admitted to Dhaka Medical College Hospital were due to asthma[4].

The cause of asthma is still not certain though theories abound. One of the most characteristics featurs of asthma is airway hyperresponsiveness, which is an exaggerated bronchoconstrictor response to a variety of inhaled stimuli, including histamine, cholinergic agonists, cold air, nonisotonic agonists, cold air, nonisotonic solutions, inertdust, sulphurdioxide, allergens. Any theory of asthma may explain this abnormal response[5,6]. Aerosol broncholilators are important therapy for patients with asthma[7]. In asthma bronchodilator therapy is the main stay of treatment. It is found that bronchodilator given by aerosols are superior to systemic therapy with the same agents.

The present study was designed to see the effects of inhaled salbutamol and ipratropium bromide individually and in combinations in bronchial asthma and to see what further improvement could be obtained with inhaled steroid in addition to both drugs. In this study an

1. Assistant Professor, IDCH Dhaka, 2. Assistant Professor, IDCH Dhaka, 3. Assistant Professor, IDCH, Dhaka, 4. Director IDCH, Dhaka

attempt was made so that an uniformly effective therapy may be established for bronchial asthma patients and the sufferings of the patients may be alleviated.

Materials and Methods :

The study was a prospective single blind case controlled study done in IDCH Mohakhali Dhaka. A total number of 29 patients were included in the study. The diagnosis of asthma followed the previously agreed criteria[7]. Only clinically clean cases were included. Significantly disabled patients due to asthma and patients with diabetes mellitus, heart failure, chronic renal failure, Ischaemic heart disease pregnancy and corpulmonalae were excluded from the study.

Treatment regimens comprised four consecutive 3 day period after a pretrial 2 day assessment.

Regimen I

First salbutamol or ipratropium bromide anyone was given by random selection than alternate drug was given.

Regimen II

Salbutamol and ipratropium bromide was given together.

Regimen III

Salbutamol, ipratropium bromide and beclomethasone was given.

Allocation to the order of sabutamol or ipratropium in the first two treatment period was by random selection with each drug given singly. Thereafter salbutamol and ipratropium bromide were given together and whichever drug was administered in the first 3-day treatment was with salbutamol, ipratropium bromide and beclomethasone. Salbutamol given was 200μ gm ipratropium bromide 40μ gm and beclomethasone 100 gm All the drugs given at 8.00, 12.00, 18.00 and 22.00 hours daily.

Each day patients were asked if they noticed any change in their condition compared with the pretreatment state. Any untoward effects were recorded. Peak expiratory flow (PEF) was measured two times daily with wrights peak flow meter. The best of three measurements was recorded. Forced expiratory volume in one second (FEV_1) and forced vital capacity was recorded on 3rd day with spirometer. The best of three measurements was recorded.

Fishers exact probability test were used for statistical analysis. P Values <0.05 were taken as significant in all analysis

Observation and results :

Table–I shows clinical and demographic profile of patients. A total number of 29 patients

Table - I

Clinical and demographic profile of Patients

No. of patients	29
Age (in years)	
Mean	38.5
Range	20-45
Sex	
Male	18
Female	11
M : F	1.6:1
Duration of Symptoms (Years)	6.5
Mean	2-15
Range	
Severity of asthma attacks (no.of times)	4.8 (2-10)
Regular Medications	19
Theophylline	6
β_2 Agonists (oralorinhaler)	8
Cromoglycate	3
Steroids (Oral orinhaler)	2
No regular Medications	10

were included in study. The age of the patients ranged 20-55 (mean 38.5) years. Male and female ratio was 1.6:1. Number of episodic attack of severe asthma ranged 2-10 (mean 4.8) times. 19 patients were with regular medications of which 6 with theophylline, 8 beta -2 agonists 3 chromoglycate and 2 with steroids Remaining 10 patients were not with regular medications. The respiratory rate ranged 22-30 (mean 24.4) beats perminute and pulse rate ranged 90-110 (means 87) beat per minute.

Talbe II shows the pulmonary function before study. Peak expiratory flow (PEF) ranged 100-290 (mean 210.9) litre. Forced expiratory volume in one second (FEv1) ranged 0.52 - 1.2 (mean 0.92) litre and forced vital capacity (FVC) ranged 0.84-2.7 (mean 1.40) litre.

Table - II

Pulmonary functions before starting trial

Pulmonary functions	Mean ±SE	Range
Peak Expiratory flow (PEF)	210 ±10.3	100-290
Forced expiratory volume in one second (FEv_1)	0.93 ±0.12	0.52 - 1.2
Forced vital capacity (FVC)	1.40 ±0.15	0.85-2.1

Table III shows the subjective changes of symptoms with different drugs. With salbutamol 22 (75.9%) had improvement of their symptoms. With ipratroium 16(55.2%) showed improvement,with salbutamol-ipratropium it was 26(89.7%) and when beclomethasone was added with salbutamol ipratropium combination the improvement of symptoms was found to be in 29 (100%). The difference between salbutamol and ipratropium bromide combinations is significant to salbutamol and ipratropium bromide alone.On the other hand it was observed that symptoms were significantly improved when beclomethasone was added to salbutamol and ipratropium bromide combinations than combinations or either of the drug used individually.

Table–III

Subjective changes of symptoms during trial

Group	Symptoms: Improved No	Improved %	unchanged No	unchanged %
Salbutamol	a. 22	75.9	7	42.1
Ipratropium	b. 16	55.2	13	44.8
Salbutamol + Ipratropium opium	c. 26	89.7	3	10.3
Salbutamol + Ipratropium + beclome-thaspone	d. 29	100	0	0

a Vsb P = NS > 0.05 DVSa P = S<0.01
c Vsb P = S < 0.05 dvsb P = S<0.001
d Vsb P = NS> 0.05 CVSa P = NS> 0.05

Table IV shows the changes in pulmonary function after different therapy.The increase in PEF to salbutamol and iratropium are insignificant (P = Ns). There is significant increase in PEF (P<0.01) with combinations of salbutamol and ipratropium than to ipratropium alone. There is no significant increases in PEF (P>0.05)when beclomethasone was added with salbutamol ipratropum combinations to combinations alone and to salbutamol sused individually but in comparison to ipratropium alone it is highly significant (P<0.001) changes in PEF with combinations to salbutamol alone is insignificant (P>0.05).

Table-IV

Effective of treatment on pulmonary functions

	PEF	FEV_1	FVC
Salbutamol	275 ± 11.21	1.50± 0.18	1.95 ± 0.22
Ipratropium	246 ± 10.74	1.25 ± 0.16	1.72 ± 0.18
Salbutamol + Ipratropium	290 ± 9.94	1.85 ± 0.25	2.40± 0.27
Salbutamol + Ipratropium + beclomethasone	302 ± 10.33	2.75 ±0.28	3.25 ± 0.30

There is no significant change (P<0.50) in FEV_1 (in table-IV) when ipratropium and salbutamol used individually as well as salbutamol to salbutamol-ipratropium combinations (P<0.50). Changes in FEV_1 with combinations to ipratropium alone is significant (P<0.05) Addition of beclomethasone with combinations causes significant increase in FEV_1 in comparison to combinations alone (P<0.02) as well as to salbutamol and ipratropium when used individually (P<0.02).

No significant change is observed in FVC when salbutamol and ipratropium used individually (P<0.10). The change in F VC with combinations to ipratropium alone is significant (P<0.05) but insignificant to salbutamol alone, Additions of beclomethasone causes significant increase in F VC than to combinations alone (P<0.05) as well as to salbutamol and ipratropium used individually (P<0.001).

Table V shows correlation between changes in pulmonary functions before and after treatment.

Table-V

Correlation between changes in pulmonary functions

	PEF		FEV_1		FVC	
Salbutamol	B	A	B	A	B	A
	210.9 ± 103	275±11.21 P<0.001	0.93 ± 0.12	1.50 ±0.18 P<0.01	1.4 ±0.15	1.95±0.22 P<0.05
Ipratropium	210.9 ± 10.3	246 ± 10.74 P<0.05	0.93 ± 0.12	1.25 ±0.16 P>0.05	1.4 ± 0.15	1.72 ±0. 18 P>0.05
Salbutamol + Ipratropium	210.9±10.3	290 ±9.94 P<0.001	0.93±0.12	1.85 ± 0.25 P<0.01	1.4 ± 0.15	2.40 ± 0.27 P<0.001
Salbutamol + Ipratropium + beclometh one	210.9 ± 103	302 ± 10.33 P<0.001	0.93± 0.12	2.75 ± 0.28 P<0.001	1.4 ± 0.15	3.25 ± 0.30 P<0.001

* B = Before trial * A = After trial

All components of pulmonary functions shows significant changes with salbutamol. With iopratropium changes in FEV_1 and FVC is not significant. With combinations all components of pulmonary function shows significant improvement. Significant improvement of pulmonary functions also noted when beclomethasone was added to salbutamol-ipratropium combinations.

Discussion :

Bronchial asthma is a common disease in Bangladesh. A survey in a defined population of persons aged 15 years or above in Bangladesh, the prevalence of bronchial asthma was found to be 3 per 1000. This is the highest reported incidence figure[8]. It was found that most of the patients were in fourth decades of life. Although asthma afflicts men and women equally after the age 30.9, the overall male female ratio in this study was 1.6:1. This apparent discrepency might be explained by the numerical superiority of males compared to the female who receive treatment from the hospital. It also reflects the general tendency of our woman folk to refrain from seeking medical help.

PEF,FEV_1,FVC are affected in asthma and is due to narrowing of airways at all levels. Changes in PEF observed in this study also found in other study[10]. Salbutamol produces bronchodilatation by stimulating beta adrenergic receptors in bronchial muscles and ipratropium works by blocking vagal reflexes. The combinations of the two drugs produce a slightly greater and more prolonged response than either alone[10]. In mild asthma salbutamol may produce almost complete bronchodilatation, so that a second or third drug has no opportunity of showig its worth.The position may be different in more severe asthma[11].

The FEV_1 represents the integrated flow over the first second of expiration and reflects airway narrowing during expiration. It is relatively independent of effort unlike PEF. In any cause of airflow obstruction the FEV_1 is reduced. Ullah et al[12] showed that the effects of beta. 2 agonists and the anti cholinergic drugs are independent and additive.This additive effect also observed in this study. Addition of beclomethasone to salbutamolipratropium combinations in this study showed a significant increase in FEV_1 other study also showed increase in FEV_1 with steroid[12,13].

In any case of airflow obstruction to a lesser extent the FVC is also reduced. In this study changed in FVC was noted with bronchodilator and steroid. Such observation also noted in other study[14].

When pretrial and post trial values of pulmonary functions were correclated it was found that with salbutamol pulmonary functions improved significantly, with ipratropium PEF was significantly improved, FEV_1 and FVC showed only numerical improvement. WIth salbutamol-ipratropium and Beclomethosone-salbutamol ipratropium pulmonary functions improved significantly.

Conclusion :

It can be concluded that both salbutamol and ipratropium produces approximately equal clinical improvements in bronchial asthma, salbutamol showing advantage in improving pulmonary functions over ipratropium. The combinations of both drugs together have additive effect. This additive effect will make it logical to use safe dose of individual drugs in combination rather than increasing individual drugs dosage to possible toxic levels. This summation of improvement may well be the future role for this new anticholinergic drugs. Adiction of beclomethasone to both will have only marginal advantage than combination of both drugs.

References :

1. Sanjoy Grag et al : Clinical ventilatory functions and immunological studies in bronchial asthma. J. Indian Med. Associ: 1991; 89 (1): 6-12.
2. Daniel R.P.Asthma In Wyngarden JB and Smith LH (eds). Cecil Text book of Medicine 18th ed. Philadelphia; WB Saunders, 1988; 403-410.
3. Valman H B Bronchial asthma. Br. Med. J. 1987:294:753-7.
4. Khan AK, Haque ME, prevalence of respiratory disease in adult patient in consultation and Hospital practice. Chest and Heart Bulletin :1986; x(2): 29-33.
5. Barnes P J Mechanism of Asthma.

   Medicine International : 1991:4:3694-98.
6. Michael T, Myrna B. Control of asthma by aerosols. The new Eng J of Med : 1986; 314 : 870-73.
7. Ciba guest symposium Terminology, Definitions and classifications of chronc pulmonary emphysema and related conditions. Thorax 1959; 14 : 286.
8. Rahman SM. Retrospective study of bronchial asthma. Dissertation 1981; 1.
9. Spector SL. Definition of Asthma, ATS News, Fall 1982:8:5.
10. Petric GR. Palmer KNV comparison of aerosol ipratropium bromide and salbutamol in chronic bronchitis and asthma. Dr. Med J 1975; 1: 430-432.
11. Ward MJ, Fentem PH, Ipratropium bromide in acute asthma. Br. Med J. 198; 282 : 598.
12. Collins JV, clark TCH The use of corticosteroids in the treatment of acute asthma. Quarterly J If Med. 1975; 174 : 259-73.
13. Ullah et al, Influence of age on response to ipratropium and salbutamol in asthma. Thorax 1981: 36: 523.
14. Higgins TT. Respiratory symptoms and ventilatory capacity Br. Med. J. 1959; 1:325.